IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NOVARTIS PHARMACEUTICALS CORPORATION and ASTEX THERAPEUTICS LTD. Plaintiffs, v. MSN PHARMACEUTICALS INC. and MSN LABORATORIES PVT. LTD., Defendants.	C.A. No. 21-870-GBW (CONSOLIDATED) [redacted] **REDACTED VERSION**

MSN'S REPLY POST-TRIAL BRIEF

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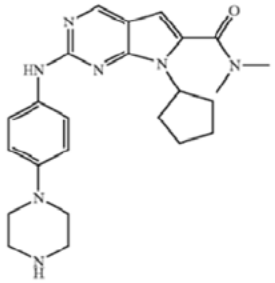
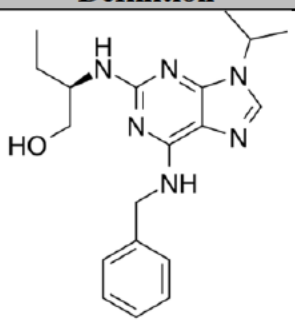
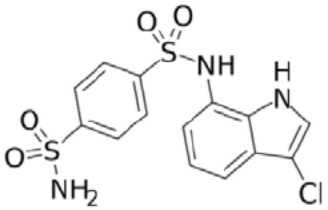
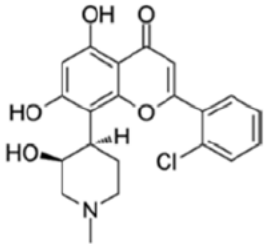
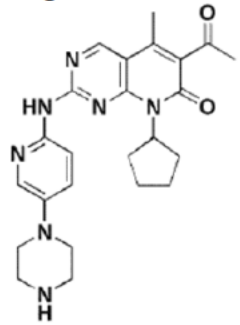
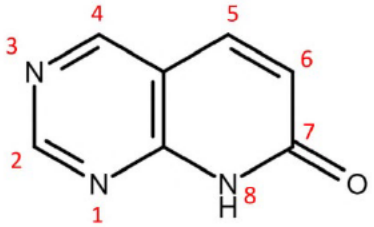
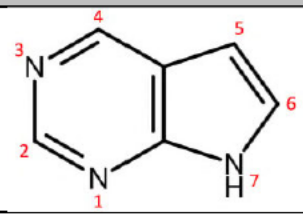
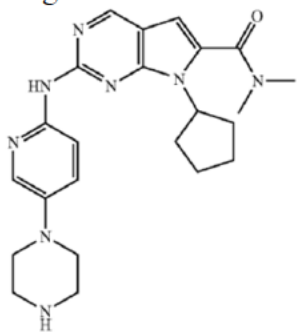
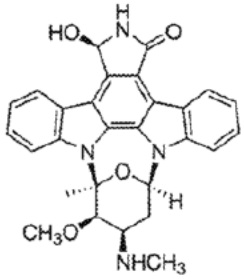
GLOSSARY

Term	Definition
'225 Patent	U.S. Patent No. 8,324,225 (JTX0001)
'355 Patent	U.S. Patent No. 8,415,355 (JTX0002)
'630 Patent	U.S. Patent No. 8,962,630 (JTX0004)
Abemaciclib	The active ingredient in Eli Lilly's Verzenio® product (JTX0113)
ANDA	Abbreviated New Drug Application
Asserted Claims	Claim 1 of the '225 Patent Claim 1 of the '355 Patent Claim 6 of the '630 Patent
Asserted Species Claims	Claim 1 of the '355 Patent Claim 6 of the '630 Patent
Asserted Patents	The '225, '355, and '630 Patents
Astex	Astex Therapeutics Ltd.
Barvian	Mark Barvian et al., *Pyrido [2,3-d] pyrimidin-7-one Inhibitors of Cyclin-Dependent Kinases*, 43 J. Med. Chem. 4606-4616 (2000) (JTX0021)
Brain PCT	WO 2007/140222 (JTX0042)
CDK4	Cyclin-dependent kinase 4 and/or cyclin-dependent kinase 6
Chen	U.S. Patent Application Pub. No. 2003/0207900 (JTX0041)
Choi	WO 2005/080393 (JTX0142)
Choi (I) 2006	Ha-Soon Choi et al., *Design and synthesis of 7H-pyrrolo[2,3-d]pyrimidines as focal adhesion kinase inhibitors. Part I*, 16 Bioorganic Med. Chem. Lett., 2173-2176 (2006) (JTX0153)
Choi (II) 2006	Ha-Soon Choi et al., *Design and synthesis of 7H-pyrrolo[2,3-d] pyrimidines as focal adhesion kinase inhibitors. Part 2*, 16 Bioorganic Med. Chem. Lett., 2689-2692 (JTX0154)
Compound 338	Compound illustrated in Example 338 of Brain PCT, having the structure:  (*See* JTX0042-0152)
CYC-202	CDK2 inhibitor developed by Cyclacel that advanced to phase II clinical trials in the early 2000s, having the structure:

Term	Definition
	 (*See* JTX0177-0006, Table 1)
CDK	Cyclin-dependent kinase
E7070	CDK2 inhibitors developed by Eisai that advanced to phase II clinical trials in the early 2000s, having the structure:  (*See* JTX0177-0006, Table 1)
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
Flavopiridol	First CDK inhibitor to enter clinical trials, developed by Sanofi-Aventis, having the structure:  (*See* JTX0177-0006, Table 1)
HR+	Hormone receptor-positive
HER2-	Human epidermal growth factor receptor 2 negative
hERG	Human ether-a-go-go-related gene
IC_{50}	Half-maximal inhibitory concentration
Italicized text	All emphasis added except where noted otherwise
JAK3	Janus kinase 3. A type of non-receptor tyrosine kinase
Kisqali	To include both Kisqali® and Kisqali® Femara® Co-Pack (except where differentiated), drug products approved by the FDA in 2017 for the treatment of adult patients with HR+/HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant and marketed by Plaintiff Novartis. Ribociclib is an active ingredient in Kisqali® and Kisqali® Femara® Co-pack.

Term	Definition
LEE011	Novartis internal designation for compound now known as ribociclib.
µM	Micromolar
mBC	Metastatic Breast Cancer
MSN	Defendants MSN Pharmaceuticals Inc. and MSN Laboratories Pvt. Ltd.
NBRx	New-to-brand prescription
NCCN	National Comprehensive Cancer Network
Novartis	Plaintiff Novartis Pharmaceuticals Corp.
OS	Overall Survival
OTDP	Obviousness-type double patenting
P38	A type of mitogen-activated protein kinase
Palbociclib	The active ingredient in Pfizer's Ibrance® product, a pyridopyrimidinone having the structure:  (*See* JTX0258-0014)
Pfizer SAR Papers	Barvian, Toogood 2001, VanderWel, and Toogood 2005, collectively
Plaintiffs	Novartis Pharmaceuticals Corporation and Astex Therapeutics Ltd., collectively
POSA	Person of ordinary skill in the art
PTO	United States Patent and Trademark Office
Pyridopyrimidinone (6,6-pyridopyrimidinone)	A fused 6,6 bicyclic compound having the core structure shown below (atom numbers shown in red), which can be substituted: 
Pyrrolopyrimidine (6,5-pyrrolopyrimidine)	A fused 6,5 bicyclic compound having the core structure shown below (atom numbers shown in red), which can be substituted:

Term	Definition
	
QOL	Quality of life
Ribociclib (LEE011)	The active ingredient in Novartis's Kisqali® product, and a pyrrolopyrimidine having the structure:  (*See* JTX0081-0016)
SAR	Structure-activity relationship
Selectivity	Ratio of inhibitor activity against desired target relative to inhibitor activity against non-target
Toogood 2001	Peter L. Toogood, *Cyclin-Dependent Kinase Inhibitors for Treating Cancer*, 21(6) Med. Res. Rev., 487-498 (2001) (JTX0096)
Toogood 2005	Peter L. Toogood, *Discovery of a Potent and Selective Inhibitor of Cyclin-Dependent Kinase 4/6*, 48 J. Med. Chem., 2388-2406 (2005) (JTX0094)
Tr.	Final trial transcript
UCN-01	CDK inhibitor that advanced to phase II clinical trials in the early 2000s, having the structure:  (*See* JTX0177-0006, Table 1)
VanderWel	Scott N. VanderWel et al., *Pyrido[2,3-d] pyrimidine-7-ones as Specific Inhibitors of Cyclin-Dependent Kinase 4*, 48 J. Med. Chem. 2371-2387 (2005) (JTX0099)

I. INTRODUCTION

None of Plaintiffs' arguments overcome MSN's strong showing that a POSA would have been motivated to install the pyridyl nitrogen on Compound 338 to achieve ribociclib, with more than a reasonable expectation of success. Further, none of the purported secondary considerations mitigate the obviousness of that modification. The Asserted Species Claims should be found obvious.

Plaintiffs' arguments on enablement and written description for the '225 patent are unsupported by relevant case law and the facts. The specification does nothing to show the inventors were in full possession of the claimed genus, and Plaintiffs cherry-pick from laundry lists of substituents to try to find written description. And differentiating the useful compounds in claim 1 from the useless ones would require undue experimentation. The claims are invalid.

II. THE ASSERTED CLAIMS ARE OBVIOUS OVER COMPOUND 338 IN VIEW OF THE PFIZER SAR PAPERS

Plaintiffs concede that Compound 338 is admitted prior art. D.I. 138, 15. However, Plaintiffs disagree with MSN as to the scope of the admission. *See* D.I. 138, 18-20. But Plaintiffs' efforts to limit the scope of the admission are unavailing. Nor has Plaintiff rebutted MSN's strong showing that a POSA would have selected Compound 338 for further modification, and that installing the pyridyl nitrogen to achieve ribociclib would have been exceedingly obvious.

A. Compound 338 And The Explanatory Disclosure Of Its Use As A CDK Inhibitor Is Within The Scope Of The Admitted Prior Art.

Compound 338 and the explanatory disclosure of its use as a CDK inhibitor (*e.g.*, in Table 4 of the '355 and '630 patents) is within the scope of the admitted prior art. D.I. 135, 7-8. Plaintiffs, without citing any evidence or supporting law, baldly state that "the statement [identifying Compound 338 as among the "closest prior art"] . . . should carry no weight," and that "the admission extends only to the structures of those [admitted prior art compounds] and does not

include any of the data reported in Brain [PCT]." D.I. 138, 15-16. But this argument fully contradicts Plaintiffs' new admission that "Brain [PCT] and all of the compounds disclosed therein, including Compound 338, are in the prior art." *Id.*, 15. Plaintiffs' self-contradictory arguments should be dismissed.

Separately, Plaintiffs argue that the IC50 data in Table 4 of the '355 and '630 patents[1] is not within the scope of the admitted prior art. *See id.*, 18-20. But Plaintiffs' analysis of *Nomiya* is misleading. In fact, *Nomiya* held that both Figs. 1 and 2 *and the statements about the figures* in the specification were admitted prior art. The full quotation selectively edited by Plaintiffs states: "Therefore, on this record, the admission is only that the structure shown in Figs. 1 and 2 … ***and the use of that structure in a dynamic shift register circuit*** were known to the art when appellants invented their improvements." *In re Nomiya*, 509 F.2d 566, 571 (C.C.P.A. 1975); *see also id.* at 571 n.6 ("The application contains a section entitled 'Description of the Prior Art,' which explains Figs. 1 and 2 in detail."). Thus, *Nomiya* squarely supports MSN's position that Compound 338 and the explanatory disclosure of its use as a CDK inhibitor (*e.g.*, in Table 4) is within the scope of the admitted prior art.

PharmaStem also supports MSN. *See* D.I. 135, 8. Plaintiffs concede that the *PharmaStem*

[1] Plaintiffs assert that MSN's discussion of the Table 4 data is "entirely new." D.I. 138, 10. Not so. As early as its Notice Letter, MSN stated that, "While a POSA could have chosen from several lead compound candidates identified in the prior art, a POSA would have been highly motivated to consider Compound 338 of Brain [PCT], ***including based on its inhibitory activity and selectivity to Cdk4***. *See* Brain [PCT] at 197. ***This compound is admitted prior art in the '355 patent (see '355 Patent at 17:34-18:60, "compound 200"), with an IC50 of 0.005 µm against Cdk4***." FOF, ¶83. MSN's Invalidity Contentions also state that, "A POSA could have obtained ***more exact IC50 values for [Compound 338], like those in the '355 Patent***, without an undue burden." *Id.* In his expert reports, Dr. Micalizio analyzed obviousness to the extent that Compound 338 and the other compounds in Brain PCT were admitted prior art, but he properly did not opine on the legal question of what specific disclosure in the '355 and '630 patents was or was not prior art (*see, e.g., TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004)). *Id.* Plaintiffs' assertion is unfounded.

"court found that ***characteristics of the prior art in the specification*** are binding on the patentee …." D.I. 138, 19. That's exactly the point here. The admissions in the '355 and '630 patents include the prior art compounds themselves and the characteristics of the prior art in the specification (*i.e.*, the disclosed use as CDK inhibitors). And in line with the *Hellsund* case Plaintiffs cite, MSN only attributes as admitted prior art "the portion referenced as prior art …." *See id.*, 19-20 (*citing Application of Hellsund*, 474 F.2d 1307, 1311 (C.C.P.A. 1973)).[2]

Plaintiffs further argue, without testimonial evidence, that the IC50 data in Table 4 is not prior art because it "is included to establish the unexpected results demonstrated by ribociclib in comparison to Compound 338." D.I. 138, 20 (citing JTX0002). But even if the data was intended to establish unexpected results, this does not change the fact that Table 4 clearly labels Compound 338 as a "prior art" comparator. And for this data to support unexpected results (as Plaintiffs argue), a POSA would have needed to know the IC50 data in the prior art at the time of the application, in order to compare "expected" and "unexpected" results. *See Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019) (reversing district court holding of unexpected results because a POSA would not have known what was expected based on the prior art). Thus, Plaintiffs' "unexpected results" argument tacitly acknowledges that the IC50 data in Table 4 is within the "expected" results in the prior art.

B. <u>A POSA Would Have Selected Compound 338 As A Lead For Modification.</u>

MSN showed why a POSA would have selected Compound 338 as a lead for modification. D.I. 135, 8-9. In rebuttal, Plaintiffs present a laundry list of several alternatives that a POSA may have selected instead. *See* D.I.138, 14. But Dr. Toogood agreed at trial "that the prior art can point

[2] As Plaintiffs correctly noted, Dr. Micalizio "did not rely" on the Table 4 data for his lead compound analysis. *See* D.I. 138, 10. Rather, Dr. Micalizio opined the IC50 data in Table 4 is consistent with the data disclosed in Brain PCT, and together with the Pfizer SAR Papers, would have motivated a POSA to select Compound 338 for further modification. D.I. 135, 8-9.

to more than one lead compound for further development efforts." FOF, ¶84. Thus, the mere existence of other potential leads is irrelevant to whether Compound 338 would have been selected.

Plaintiffs focus in particular on palbociclib, claiming that Dr. Micalizio "ignored" it. D.I. 138, 14. Not so. Dr. Micalizio not only testified that he considered palbociclib as *one* lead, but also how it would guide a POSA to consider Compound 338 a lead, too. FOF, ¶85. And MSN heavily relies on the Pfizer SAR Papers, which disclose that palbociclib is a "remarkably potent and selective" CDK4 inhibitor. *See* D.I. 135, 8. There is no requirement "that the prior art must point to only a single lead compound for further development efforts." *Altana Pharma AG v. Teva Pharms. USA, Inc*., 566 F.3d 999, 1008 (Fed. Cir. 2009). The Pfizer SAR Papers, and palbociclib in particular provide ample motivation to select Compound 338 as a lead. *See* D.I. 135, 8-9. Thus, MSN far from "ignore[s]" palbociclib. *See* D.I. 138, 14.

Refocusing on Compound 338, Plaintiffs next argue that a POSA would not have arrived at Compound 338 "From Brain [PCT]." D.I. 138, 17. But MSN never argued that a POSA would have selected Compound 338 based on Brain PCT alone; rather, a POSA would have selected it based on the Pfizer SAR Papers as well. D.I. 135, 9.[3] And even if one were to consider the CDK4-potent compounds from Brain PCT in a vacuum, Dr. Toogood admitted that "there's no reason to include or exclude any of these compounds from consideration" if one was looking to provide selectivity against other CDKs. FOF, ¶84.

Plaintiffs assert that Dr. Toogood "*directly* rebutted" Dr. Micalizio's testimony on the four

[3] Attempting to revive their denied motion *in limine*, Plaintiffs again assert that MSN proffered a "new" lead compound analysis "that starts with Compound 338 divorced from Brain [PCT]'s disclosure." *See* D.I. 138, 9-10. As MSN stated in its Response, "Plaintiffs have had ample notice of MSN's contention that the '355 and '630 patents are obvious over Compound 338," and "MSN's notice letters, contentions, and expert reports … identify Compound 338 as admitted prior art." FOF, ¶83.

key regions in which a compound's structural motifs interact with the CDK4 enzyme, as shown in the Pfizer SAR Papers. *See* D.I. 138, 18 (emphasis in original). But Plaintiffs only presented hypothetical modifications that could have been made to a compound's core or side groups, and never rebutted Dr. Micalizio's testimony that a POSA would have expected Compound 338 to interact with the four key regions in the same way as the compounds in the Pfizer SAR Papers. FOF, ¶86. Plaintiffs' further argument that "[t]he Pfizer SAR Papers do not provide any suggestion that their teachings could apply to 6,5-pyrrolopyrimidines" is the type of overly-cramped view of the prior art the Supreme Court and Federal Circuit have rejected. *See Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 931 (Fed. Cir. 2024) (finding legal error under *KSR Int'l Co. v. Teleflex Co.*, 550 U.S. 398, 418 (2007), for failure to consider "'interrelated teachings of multiple' references, 'the background knowledge possessed by a [POSA],' or 'the inferences and creative steps that a [POSA] would employ.'").

C. A POSA Would Have Been Motivated To Modify Compound 338 To Achieve Ribociclib, With More Than A Reasonable Expectation Of Success.

MSN showed how a POSA would have been motivated to put the pyridyl nitrogen (*i.e.*, the "magic N") on Compound 338 to achieve ribociclib, with more than a reasonable expectation of success. D.I. 135, 9-11. Plaintiffs proffer four arguments in rebuttal. *See* D.I. 138, 20-24. All fail.

First, Plaintiffs argue that MSN "failed to demonstrate a motivation to modify Compound 338." *Id.*, 20. Yet, Plaintiffs again myopically view Compound 338 via Brain PCT alone, and neither consider the additional teachings of the Pfizer SAR Papers, nor Dr. Micalizio's unrebutted testimony that a POSA would have expected Compound 338 to interact with the CDK4 enzyme in the same way as Pfizer's compounds. *See* D.I. 135, 8-9; FOF, ¶ 41. Plaintiffs' citation to *Onyx* is unhelpful. *See* D.I. 138, 21 (*citing Onyx Therapeutics Inc. v. Cipla Ltd.*, 613 F.Supp. 3d 817, 855-56 (D. Del. 2020)). In that case, the art did not point to the exact, proposed modification. Here,

one of the Pfizer SAR Papers, Toogood 2005, made it clear that the pyridyl nitrogen, the sole modification of Compound 338 needed to achieve ribociclib, conferred a high level of selectivity that "appears to be general and to apply across a wide range of kinases." FOF, ¶ 39.

Second, Plaintiffs propose that "there were numerous modifications that a POSA could have made" to Compound 338. D.I. 138, 21. But Plaintiffs continue to ignore the one modification, the pyridyl nitrogen, that Toogood 2005 singled out as conferring high selectivity. FOF, ¶ 39.

Third, Plaintiffs rehash that a POSA had no reasonable expectation that the Pfizer SAR Papers could apply to the 6,5-pyrrolopyrimidine scaffold of Compound 338. D.I. 138, 22. But, as noted *supra*, Plaintiffs' cramped reading of the Pfizer SAR Papers flouts *KSR* and its progeny, and does not account for Dr. Micalizio's unrebutted testimony to the contrary. *See* FOF, ¶ 41.

Fourth, Plaintiffs proffer that "the Pfizer SAR Papers teach different modifications that a POSA could have made to improve potency, which Dr. Micalizio ignored." D.I. 138, 22-24. But "[a] POSA can be motivated to do more than one thing," and there is no requirement the proposed modification be the *only* thing motivating a POSA. *Janssen Pharms.,* F.4th at 930. Nevertheless, a POSA was not directed to those other modifications. As an example, Plaintiffs cite Toogood 2001 for a proposed modification to increase the size of the cycloalkyl group at N8. D.I. 138, 22-24. But Plaintiffs disregard that Toogood 2005, published later, concluded that the smaller cyclopentyl at N8 "provided the best combination of potency and selectivity" for CDK4. FOF, ¶87. Dr. Toogood admitted that "a later publication [in the Pfizer SAR Papers] might restate or revise a perspective on an earlier … publication …." *Id*. Such was the case here.

Plaintiffs argue that a POSA would have been dissuaded from incorporating the pyridyl nitrogen because it led to a decrease in potency for CDK4 with palbociclib. D.I. 138, 23. But Plaintiffs ignore that the Pfizer SAR Papers teach that there was "a subtle balance between the two

desirable properties of selectivity and potency," which "suggested that the optimal inhibitor may not be the most potent." FOF, ¶ 44; *see also* Tr. 470:10-15. Plaintiffs also ignore that, despite this decrease in potency, the Pfizer SAR Papers praise palbociclib as displaying "a superior overall profile, including the combined attributes of potency, selectivity, and pharmaceutical properties." FOF, ¶ 39. And even if the mechanism behind the pyridyl nitrogen was "'not understood' at that time" (D.I. 138, 23),[4] Toogood 2005 discloses that it conferred high selectivity that "appl[ies] across a wide range of kinases," which would have motivated a POSA to use it. FOF, ¶ 39.

Finally, Plaintiffs assert that, instead of installing the pyridyl nitrogen, "a POSA would have first considered adding a methyl group at the C5 position." D.I. 138, 24. But, as Dr. Micalizio explained at trial, Toogood 2005 shows that high levels of selectivity can be achieved by installing the pyridyl nitrogen "without having a C5 methyl." FOF, ¶88.

None of Plaintiffs' arguments overcome MSN's strong showing that a POSA would have been motivated to install the pyridyl nitrogen on Compound 338 to achieve ribociclib, with more than a reasonable expectation of success.[5]

D. MSN Did Not Engage In Hindsight Analysis Or Rely On Novartis Documents.

Plaintiffs protest that MSN "impermissibly relies on internal Novartis documents and the inventors' own path *as evidence of obviousness*." D.I. 138, 24. A cursory reading of MSN's Opening Brief squelches such argument. MSN restricts its citations to Novartis documents to the background Section 1.B. (*see* D.I. 135, 3-6) discussing Novartis' path to ribociclib; however, no Novartis documents are "relie[d] on" (or even cited) in the remainder of the Opening Brief. *See*

[4] Plaintiffs misleadingly imply that Toogood 2005 states that "it would be hard to extrapolate [the pyridyl modification] to an entirely different core and expect it to be understood." *See* D.I. 138, 23. However, this quote is properly attributed to Dr. Toogood's testimony. *See* Tr. 397:16-18.

[5] In their brief, Plaintiffs only assert that claim 6 of the '630 patent was nonobvious on the grounds that ribociclib was nonobvious. *See* D.I. 138, 32. Thus, the Asserted Species Claims fall together.

D.I. 135, 6-24. Plaintiffs also make the silly argument that because MSN used the Novartis-coined term "magic N" to describe the pyridyl nitrogen modification, MSN relied on non-prior art to make its obviousness case. *See* D.I. 138, 24. But nobody disputes that Novartis' nickname stemmed from the prior art Toogood 2005, which disclosed that the pyridyl nitrogen conferred a high level of selectivity. *See* FOF, ¶¶16, 89. And MSN does not argue that "Novartis['] motivat[ion] to develop a 'fast follower' compound" (*see* D.I. 138, 24) was something that would have motivated a POSA to select Compound 338 or modify it to install the pyridyl nitrogen.

In an attempt to rewrite history, Plaintiffs assert that "[r]ibociclib's 6,5-pyrrolopyrimidine core was not selected because of its 'close structural similarity to palbociclib.' Instead, this was a breakthrough arising from the surprising discovery that pyrrolopyrimidines from Novartis's JAK3 program could be potent and selective CDK4 inhibitors." D.I. 138, 25 (citation omitted). In so arguing, Plaintiffs wish to substitute Dr. Brain's contemporaneous characterization with Dr. Toogood's *ex post facto*, paid opinion. *Compare* JTX0022-0001 (Dr. Brain stating "your compounds bear a close similarity to a competitor series that Pfizer have developed…") *with* Tr. 421:2-421:6 (Dr. Toogood testifying: "Q: And based on this kind of data, would it have been predictable that [] a [pyrrolopyrimidine] core would be a potent and selective CDK 4 inhibitor? A: No. That would not have been predictable based on this data."). Plaintiffs' litigation-oriented, hindsight attempts to change history should be denied.

MSN neither engaged in hindsight nor relied on Novartis' documents in making its obviousness case. In contrast, Plaintiffs dedicate four pages of their Brief to discussing "the development history of ribociclib" in an attempt to demonstrate "that drug discovery is generally unpredictable." D.I. 138, 26. But that entire process of drug discovery has no bearing on whether a POSA would have modified prior art Compound 338 with Toogood 2005's pyridyl nitrogen with

a reasonable expectation of success. That, instead, is a single modification to "a prior art compound that a POSA would know and a . . . molecular change in that prior art compound that was taught by the prior art." FOF, ¶90. Moreover, Novartis' path simply has no bearing on the obviousness inquiry here: "while patentability of an invention is not negated by the manner in which it was made, the converse is equally true: patentability is not imparted where the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1369 (Fed. Cir. 2007). The Asserted Claims are invalid as obvious.

E. Secondary Considerations Do Not Support Nonobviousness.

Plaintiffs' assertions of secondary considerations do not overcome the *prima facie* case of obviousness, because Plaintiffs' arguments lack the appropriate context, rely on incorrect legal standards, and fail to show a nexus. Moreover, Plaintiffs improperly rely on new arguments and expert opinion offered for the first time at trial.

Contrary to Plaintiffs' allegations, MSN contests any nexus between the Asserted Claims and the marketed product, KISQALI. There is no presumption of nexus here, because the Asserted Claims are not "coextensive" with the marketed product. *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1360-63 (Fed. Cir. 2021). Plaintiffs and their experts failed to attribute unasserted patents listed in the Orange Book and KISQALI's required co-administration with hormone therapies. FOF, ¶¶57, 91. Accordingly, none of the secondary considerations offered can rebut the obviousness of the Asserted Claims.

1. Ribociclib fails to show any unexpected benefit under the correct legal standard.

Plaintiffs' assertions of unexpected results are based upon the expected and predictable inherent features of ribociclib and the unsubstantiated "superiority" of KISQALI. For a property

or result to be probative for nonobviousness the property must be both superior *and* unexpected. *Pfizer*, 480 F.3d at 1371. Plaintiff failed to show either of these. Superiority of an alleged unexpected result is shown by comparing the alleged benefits of the claimed invention to the closest prior art. *In re De Blauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Thus, although post-issuance evidence has been permitted, "the results must be 'unexpected by one of ordinary skill at the time of [the] application.'" *Forest Labs.*, 918 F.3d at 937; *Pfizer*, 480 F.3d at 1371.[6]

By Plaintiffs' own admission, Compound 338 is one of three compounds constituting the "closest prior art." FOF, ¶22. Therefore, only comparing ribociclib to Compound 338 is probative for nonobviousness. Compound 338 showed CDK4-potency and its selectivity profile was well-understood. *Id.*, ¶¶27-28. A POSA would have expected installing the "magic N" on Compound 338 to achieve ribociclib would maintain potency while substantially improving selectivity. *Id.*, ¶92. Indeed, that expectation was borne out. Even if ribociclib's selectivity compared to Compound 338 was unexpected, it is a difference in degree, not kind: both compounds showed potency and selectivity for CDK4. *Id.* at ¶¶29-32, 35-36. The record evidence does not show "a new property dissimilar to the known property," but rather—***at most***—shows "a predictable result to an unexpected extent." *UCB, Inc. v. Actavis Labs. UT, Inc.*, 65 F.4th 679, 693-95 (Fed. Cir. 2023) (internal citations omitted).

Plaintiffs' alleged unexpected medical benefits are also not probative of nonobviousness, because Plaintiffs apply the incorrect legal standard and fail to consider all of the evidence. Plaintiffs compare KISQALI's OS clinical trial results to those of palbociclib. D.I. 138, 28. However, as Plaintiffs admit, palbociclib is not the closest prior art, even if it is "a proper lead compound." *Id.*, ¶22. Accordingly, these alleged benefits are not applicable as a matter of law. *De*

[6] Responding to the Court's legal standard inquiry at trial. Tr. 827:1-11.

Blauwe, 736 F.2d at 705. But even if KISQALI was properly comparable to palbociclib, there is no showing of unexpected results for several reasons. First, any difference in OS between ribociclib and palbociclib (each taken with a hormone therapy) is a difference in degree, not kind, because both confer a clinically meaningful improvement. FOF, ¶94. Second, a POSA would have expected a drug that meets the primary endpoint of progression free survival would also meet OS and would have been surprised if it did not. FOF, ¶93. Indeed, the experts agree that the OS from palbociclib is clinically meaningful, just as OS from ribociclib is clinically meaningful. *Id.*, ¶94. Moreover, contrary to Plaintiffs' assertions, the NCCN Guidelines do not express a preference for ribociclib; rather, the lack of head-to-head studies for CDK4 inhibitors results in *controversy* on which one to select. *Id.*, ¶96. Additionally, Plaintiffs entirely ignore that abemaciclib shows statistically significant improvement in OS in trials, and unlike ribociclib can be administered as a single agent. *Id.*, ¶95. Finally, and critically here, Plaintiffs failed to show that ribociclib's OS results were unexpected *at the time of filing the patent applications*.

2. KISQALI is not a commercial success under the proper standard.

Plaintiffs' fail to show commercial success. There is no showing of nexus, but even if there were a nexus, KISQALI consistently has less market share than its two competitors, despite KISQALI's outsized share of voice. *Id.*, ¶97. Indeed, the only metric where KISQALI "leads" is speculative. *Id.*, ¶99. Plaintiffs also ignore that expenses for KISQALI from launch through 2023 resulted in an approximately [redacted]. *Id.*, ¶98. This is the most conservative estimate [redacted] because Plaintiffs never provided evidence of KISQALI's pre-launch cost, which Plaintiffs now intimate were extensive. *Id.*; *cf.* D.I. 138, 2-6. While Plaintiffs point to total sales for KISQALI, sales data alone "provides a very weak showing of commercial success, if any." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). Finally, Plaintiffs' expert admitted that he never considered unasserted Orange Book-listed patents in his analysis, thus

failing to properly attribute KISQALI sales. FOF, ¶57. For these reasons, Plaintiffs' assertions of commercial success are not probative in the obviousness analysis.

3. Plaintiffs' newly asserted grounds for long-felt need and industry praise are improper, and there was no long-felt need or industry praise.

Before trial, Plaintiffs ***never*** disclosed an alleged long-felt need for mBC treatment with improved OS while maintaining or improving QOL, or statements from Dr. Hortobagyi and Dr. Burris to support industry praise. FOF, ¶¶53, 100. Accordingly, Plaintiffs should "not [be] allowed to use [the new] information… to supply evidence… at trial, unless the failure was substantially justified or is harmless." Fed. R. Civ. P. 26(a)(2); Fed. R. Civ. P. 37(c)(1); *O2 Micro Int'l Ltd. v. Monolithic Power Sys., Inc.*, 467 F.3d 1355, 1368-69 (Fed. Cir. 2006). The untimely disclosures cause an incurable prejudice to MSN, because MSN never had an opportunity to respond through fact or expert discovery; thus, the untimely disclosures should be excluded. *Konstantopoulos v. Westvaco Corp.*, 112 F.3d 710, 719 (3d Cir. 1997).

Nevertheless, Plaintiffs' new allegations do not support nonobviousness. Dr. Cohen was not a POSA at the time of the applications, therefore Plaintiffs' evidence of a need for mBC treatment that improved OS while maintaining or improving QOL should be dismissed. FOF, ¶¶51-53. Moreover, even if this need existed, ribociclib did not meet it, because ribociclib diminishes QOL in many patients. *Id.*, ¶101. Indeed, pre- and perimenopausal women that take KISQALI will face a severe detriment to QOL because the treatment would thrust them into menopause. *Id*. Accordingly, no alleged long felt need is met by KISQALI.

Plaintiffs' new industry praise allegations fail to consider references as a whole. The NCCN Guidelines do not "praise" KISQALI, and the NATALEE trial that *might* support a new indication for KISQALI, is an indication a competitor drug already has. *Id.*, ¶102. Neither reference shows industry praise sufficient to be probative of nonobviousness.

4. Plaintiffs' other secondary considerations rely on incorrect legal standards

Plaintiffs' conclusory arguments of skepticism should also be excluded because Plaintiffs applied the incorrect legal standard. Skepticism is not assessed as a comparison between the commercial embodiment and the prior art, but rather whether a POSA would have been skeptical that the patented invention would work as claimed. *Dow Jones & Co. v. Ablaise Ltd.*, 606 F.3d 1338, 1352 (Fed. Cir. 2010). There is no evidence under the correct standard.

Plaintiffs' assertions of failure of others and acquiescence in the industry supports are speculative and conclusory without any supporting evidence. *See Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1371-72 (Fed. Cir. 2006); *Bosch Auto. Serv. Sol., LLC v. Matal*, 878 F.3d 1027, 1037-38 (Fed. Cir. 2017) (holding mere existence of licenses or settlement alone is not probative evidence of nonobviousness). Indeed, Dr. Toogood testified he did not know the reasons why other companies halted CDK inhibitor programs, and it is undisputed that two other CDK4 inhibitors are on the market for mBC. FOF, ¶103. Plaintiffs also offered no evidence why other generic companies did not litigate the Asserted Species Claims. *Id.*, ¶104. Accordingly, Plaintiffs' evidence should not be given weight.

For these reasons, Plaintiffs' assertions of secondary considerations fall well short of relevance or reliability—both legally and factually. Accordingly, the Court should exclude and/or afford Plaintiffs no weight in its obviousness analysis.

III. THE ASSERTED SPECIES CLAIMS ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING OVER CLAIM 7 OF THE '225 PATENT.

Plaintiffs invite this Court to engage in legal error by failing to conduct an appropriate obviousness-type double patenting analysis. But the Court must both construe claim 7 of the '225 patent *and* the Asserted Claims, respectively, and then compare whether they are patentably distinct. *See* D.I. 135, 14–15. Legally, claims directed to chemical compounds extend "to any and

all such uses disclosed in the specification." *See Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1387 (Fed. Cir. 2010). Thus, MSN is not asserting that "a *POSA* would have looked to the specification of the '225 Patent to determine that the disclosed compounds could be used to inhibit CDK4 and treat breast cancer," as Plaintiffs assert, but that the Court should. Regardless, a POSA would have arrived at ribociclib and its associated method of treatment for the reasons discussed in sections II.B and C above.

IV. CLAIM 1 OF THE '225 PATENT IS NOT ADEQUATELY DESCRIBED BY THE SPECIFICATION.

Plaintiffs' arguments show exactly why claim 1 of the '225 patent lacks written description support. For instance, Plaintiffs attempt to distinguish the *University of Minnesota* case on the grounds that "the relevant disclosure there included only an extensive chemical genus, a complicated web of multiple-dependent claims, no subgenera, and—critically—no exemplary compounds falling within the scope of the claimed genus." D.I. 138, 38. But that is practically how Dr. Toogood identifies support for claim 1 in the original specification: he pieces together three different dependent claims, selects two out of twenty-three different moieties for R^{11}, selects a completely different moiety for R^{12}, and asserts the 33 compounds within the claim scope are "blaze marks" to make these choices without explanation. *See, e.g.*, D.I. 137-1 at PDX2-75-77.

Faced with this insufficiency, Plaintiffs now recast the 33 compounds as "representative species" that support a description of the claimed genus. But Dr. Toogood explicitly stated he had *no* opinion as to whether there were "representative species." FOF, ¶72. Dr. Micalizio testified—at length—that a POSA could not recognize those 33 compounds as indicating the inventors were in possession of the full claimed genus, because of the limited scope of substitution patterns at R^3, R^{13} and R^{14}. *Id.* Claim 1 is thus not adequately described.

V. CLAIM 1 OF THE '225 PATENT IS NOT ADEQUATELY ENABLED.

Claim 1 of the '225 patent is not enabled because the specification fails to teach how to make *and use* each and every member of the claimed genus. Plaintiffs admit that the specification only "identifies a utility for the claimed compounds and provides the tools to measure that utility," (D.I. 138, 39), *not* that it tells a POSA "which species ***among all those encompassed by the claimed genus*** possess the disclosed utility." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). Thus, the '225 patent "does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis. That is not sufficient." *In re '318 Pat. Infringement Litig.*, 583 F.3d 1317, 1327 (Fed. Cir. 2009). Differentiating the useful compounds included in claim 1 from the useless ones would require an iterative series of experiments for a nearly infinite number of compounds, particularly because "this art is unpredictable." FOF, ¶105. Further, the examples in the specification offer scant guidance on how to make useful compounds outside of the limited chemical space they encompass. FOF, ¶106. That, in turn, indicates undue experimentation is required to practice the full scope of claim 1. *See Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1385 (Fed. Cir. 2013). It is thus not enabled.[7]

VI. CONCLUSION

For the foregoing reasons, the Court should issue judgment in favor of MSN that claim 1 of the '355 patent, claim 6 of the '630 patent, and claim 1 of the '225 patent are invalid.

[7] Plaintiffs attempt to distinguish *Vaeck* and *Wyeth* on the grounds that the claims at issue in those cases recited "*express* functional requirements." D.I. 138, 40. But in response, Plaintiffs cite wholly inapposite cases: neither *Cortright* nor *Grunenthal GMBH* assess whether the full scope of a genus of compounds is enabled. *See In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999) and *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1346 (Fed. Cir. 2019). They thus cannot stand for the proposition that it is enough to identify an *in vitro* test that might distinguish useful compounds from useless ones, without providing further direction or guidance in the specification.

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esquire, hereby certify that on April 19, 2024, I caused to be electronically filed a true and correct copy of the foregoing sealed document with the Clerk of the Court using CM/ECF, and in addition caused true and correct copies of the foregoing sealed document to be served upon the following counsel of record by electronic mail::

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